PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The first 1000 days of life: Pre-and post-natal risk factors for morbidity and growth in a birth cohort in southern India
AUTHORS	Kattula, Deepthi; Sarkar, Rajiv; Sivarathinaswamy, Prabhu; Velusamy, Vasanthakumar; Venugopal, Srinivasan; Naumova, Elena; Muliyil, Jayaprakash; Ward, Honorine; Kang, Gagandeep

VERSION 1 - REVIEW

REVIEWER	Nita Bhandari Centre for Health Research and Development, Society for Applied Studies
REVIEW RETURNED	28-Apr-2014

| GENERAL COMMENTS | The subject is very important; few studies are available. However, the title of the project is more ambitious than the depth of the assessment as described in the manuscript.

COMMENTS

Introduction

- Too general and does not connect with the study objectives and does not clearly define the questions being answered

Methods

- Unclear how gestation was assessed.

- How were mothers followed up during the antenatal period.

- Caregivers were asked whether the child had an 'illness' and field workers were trained to use 'standard definitions'. Although the definitions of some morbidities have been provided, it is unclear how severe disease was defined and whether it is included in the presentation of illnesses. It would have been useful if standard definitions e.g. from the IMNCI were used and severe illnesses (for example, very severe disease for less than 2 months old infant and dehydration and severe pneumonia for 2 months to 24 months) were presented. The methods do however, mention using hospital discharge summaries. It needs to be mentioned clearly at the outset which illnesses have been included in the total illnesses (12803 episodes of illness)

- The rigour with which anthropometry was assessed is difficult to assess. Inter- and intra- observer standardization exercises have not been described. The type of equipment and its calibration is not |
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described. As growth has been presented only for undertwos, the term length should be used.

- Page 10: Morbidity per episode of any morbidity – what is the value of this description

- The authors have not mentioned what pre-natal maternal data are missing and reason for the missing data. Because of these missing data, risk factor analysis was done only on 216 children (over 50% loss).

- The regression model needs to be described more clearly. What were the explanatory variables; what was the time window for each.

- The rationale behind choosing a significance level of .15 in the univariate analysis to consider in the multivariate analysis is not explained. As there may be some clinically relevant variables with significant level >.15 in univariate analysis, incorporating those variables in the multivariate analysis could change the estimate of risk factors as this is an explanatory analysis.

- The authors have categorized many continuous variables to categorical variables without clear definitions such as number of household member, ANC visits, maternal age etc.

- As standard definitions for morbidity were not used, it may be difficult to generalize the findings to other settings.

REVIEWER	Prof. Somashekhar Nimbalkar
	Head, Central Research Services,
	Charutar Arogya Mandal,
	Karamsad-Anand-Gujarat
REVIEW RETURNED	30-Apr-2014

GENERAL COMMENTS	Summary: The study is a well-designed, relevant and appropriately conducted and worthy of publication. However the discussion is less engaging than you would expect from the scope of the study, especially from the Public Health viewpoint.
	Strengths: Well defined cohort, very few lost to follow up, Study variables defined sufficiently and hence it is replicable.
	Minor: Page 4, Line 18 – Use word "Economic status" instead of poverty.
	Almost 50% morbidity is due to respiratory diseases, crowding, in house smoke (40% using firewood), environmental exposures (Beedi making). These are not explored in detail. If data is available these may be explored further (unless a separate manuscript is being planned)
	It is evident that the p values changed significantly for some variables in multivariable analysis as compared to univariate analysis. It is interesting to see what emerge if factors with p less than 0.3 are included in the model (as numbers of observations are adequate for such model)
	It is interesting to observe good health seeking behavior (98% institutional deliveries) despite risk of losing daily wages. Other studies found poor health seeking behavior in urban slums. Is it due to financial independence that women enjoy in this region?
	There seems to be confusion between multivariate and multivariable. Multivariate typically implies more than two dependent

	variables. It is recommended to use 'multivariable' consistently. Diarrheal diseases and pneumonia are leading causes of morbidity and mortality in children. This is a well known fact. Even availability of potable water can reduce upto 30% disease burden in children. So the study does not show any new findings. But they are still relevant as they depict the picture in current scenario and provide guidance to policy makers and academic community on research arenas in this field. The discussion can be improved by incorporating public health interventions – current and potential ones that can be considered to address these issues. Discussion appears a replication of results and findings are compared to other studies. it does not delve enough into possible causes and potential solution. Relevance of the study to current scenario in India needs to be discussed in detail. Discussion section is the one which needs to be improve tremendously.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
Reviewer Name: Nita Bhandari
Institution and Country Centre for Health Research and Development, Society for Applied Studies,
Please state any competing interests or state 'None declared': None declared

The subject is very important; few studies are available. However, the title of the project is more ambitious than the depth of the assessment as described in the manuscript.

Response : We agree that the title is ambitious, but the purpose of the title is to focus attention on the findings of the study. Since the study does demonstrate that pre-natal factors influence birth outcomes and post-natal morbidity in the child, we would like to retain the title.

COMMENTS:

Introduction:
1. Too general and does not connect with the study objectives and does not clearly define the questions being answered.

Response: We thank the reviewer for the comment. The objective of the analysis presented in this article was to estimate the burden and assess pre- and post-natal determinants of illnesses experienced by children residing in a semi-urban slum, during the first 1000 days of life. As stated in the Methods, the objective of the funded study was to study the natural history and immune response to Cryptosporidium spp. in children from birth to 3 years of age, and the analysis presented in this paper derives from the data gathered from the cohort.
In response to the reviewer's comment, we have now restructured the Introduction focusing on the relevance of first thousand days of life in a child's development (page 4, lines 75-83) and justified the appropriateness of the study design to understand and provide better insights into complex interactions between the different domains that affect child growth and development (page 4-5, lines 84-92).
"The objective of the study was to describe the burden of morbidity, and the effect of pre- and post-natal factors on low birth weight, childhood morbidity and growth in the first 1000 days of life in a birth cohort established in semi-urban slums of Vellore in southern India." On page 5, lines 93-95.
The revised Introduction (pages 4-5, lines 67-95) reads as follows:

"The UN Millennium Development Goal 4 aims at a two-third reduction in under-5 mortality by 2015,

which includes reinforcement of efforts against pneumonia and diarrhoea, and strengthening the nutritional status of mothers and children.[1] In the past few decades, rapid urbanization, growing urban slums in developing countries, especially in India has raised concerns on public health issues such as overcrowding, lack of safe drinking water, sanitation and deprivation in multiple domains,[2-3] which in turn exposes a vulnerable age group to high risks of infectious diseases,[4] malnutrition,[5] and impaired cognitive development,[6] in the early formative years of life.

It is estimated that more than 200 million children under 5 years of age in developing countries do not attain their developmental potential.[7] The cognitive and physical development of a child is influenced by the first 1000 days of life, from conception to the second birthday.[8-10] This, in turn, is affected by biological factors such as nutrition of the mother during pregnancy, gestational age, birth weight, duration of breast feeding, childhood malnutrition, childhood infections and psychosocial factors such as economic status, parental education, and environmental exposures.[11] Often these are interdependent domains and children exposed to multiple factors are the most vulnerable. The accumulation of risk over time also compromises the overall development of the child.

Data on the burden of disease and the complex association of multiple environmental and host factors with disease are essential to permit planning of health care and prevention policies in the developing countries. Population based longitudinal/cohort studies can provide better insights into the complex interaction between the different domains affecting childhood growth and development because they capture data on disease burden at the community level, provide insights into multiple exposures in disease aetiology and help establish temporality. Longitudinal data collection overcomes the lacunae of data from cross-sectional studies, especially hospital-based studies, which reflect only the tip of the iceberg, i.e., more severe diseases, and does not provide evidence on the temporality of association. The objective of the study was to describe the burden of morbidity, and the effect of pre- and post-natal factors on low birth weight, childhood morbidity and growth in the first 1000 days of life in a birth cohort established in semi-urban slums of Vellore in southern India."

Methods:

2. Unclear how gestation was assessed.

Response: Gestation period was calculated from the last menstrual period (LMP) and the date of delivery, both of which were obtained from the antenatal cards of the mothers. This sentence has been added to the "Methods" section of the revised manuscript (page 7, line 136-138).

"Gestation period was calculated from the last menstrual period (LMP) and the date of delivery recorded on the antenatal cards."

3. How were mothers followed up during the antenatal period?

Response: During their antenatal period, the pregnant women were visited weekly by the field workers. This was done to enquire about the well being of the mothers as well as to build a rapport with the study family. This has now been stated in the "Methods" section of the revised manuscript on page 6, line 131-133.

"Before delivery, every pregnant woman was visited weekly by the field worker to enquire about her well being and build a rapport with the study family."

4. Caregivers were asked whether the child had an 'illness' and field workers were trained to use 'standard definitions'. Although the definitions of some morbidities have been provided, it is unclear how severe disease was defined and whether it is included in the presentation of illnesses. It would have been useful if standard definitions e.g. from the IMNCI were used and severe illnesses (for example, very severe disease for less than 2 months old infant and dehydration and severe

pneumonia for 2 months to 24 months) were presented. The methods do however, mention using hospital discharge summaries. It needs to be mentioned clearly at the outset which illnesses have been included in the total illnesses (12803 episodes of illness).

Response: The IMNCI guidelines are for use by health workers in resource limited outpatient settings to assess, classify and treat the sick child. The purpose of this analysis was to estimate each child's overall morbidity and not focus on severe illnesses alone or permit field workers to take responsibility for assessment or management. For morbidity surveillance, field workers were trained to use 'standard definitions' (as stated on page 8, lines 166-174) to collect information on common illnesses such as diarrhoea, cold, cough and fever. However, every time a child was sick, caregivers were encouraged to take the child to the study clinic where the illness was assessed, classified and managed by a study physician/ paediatrician, who referred severe illnesses to the hospital, if needed. Field workers were also asked to refer any children who appeared ill for whom the parents had not come to the study clinic. Overall, most parents used the study clinic for the majority of illnesses for which they sought health care.
Total illnesses/overall morbidity consisted of all episodes of gastrointestinal illnesses, upper and lower respiratory tract illnesses, undifferentiated fever, skin lesions, non-infectious illnesses and other infections such as infections of the eyes, ears or any other localized infection with or without fever. This has now been specified in the revised manuscript (page 11, line 241-244), which reads as follows:

"A total of 12,803 episodes of illness which included all episodes of gastrointestinal illnesses, upper and lower respiratory tract illnesses, undifferentiated fever, skin lesions, non-infectious illnesses and other infections such as infections of the eyes, ears or any other localized infection with or without fever were recorded during the two-year follow-up period"

5. The rigour with which anthropometry was assessed is difficult to assess. Inter- and intra- observer standardization exercises have not been described. The type of equipment and its calibration is not described. As growth has been presented only for under twos, the term length should be used.

Response: At the time of the protocol training and periodically thereafter, the field team received training on measuring the height and weight of children. Inter and intra-observer standardizations were carried out during these training workshops. As part of the study protocol, the primary caregivers were asked to bring their children to the study clinic for their monthly height and weight measurements and physical check-ups. Only in situations where the child could not be brought to the clinic, field workers took the anthropometric measurement at home. Electronic weighing scales were used to weigh the children. The weighing machines were calibrated at 6 month intervals by the Quality Assurance Department of the Christian Medical College, Vellore. We used either a length board or an infantometer to measure the length of the children.
A paragraph has been added in the "Methods" section in the revised manuscript on page 9, line 180-186.

"At the beginning of the study during the protocol training, the field team received training on measuring the height and weight of children. Inter- and intra-observer standardizations were carried out during these training workshops. Every month, weight and height/length were measured for all children at the study clinic. Only in situations where the child could not be brought to the clinic, field workers took the anthropometric measurement at home. Electronic weighing scales were used to weigh the children and a length board/infantometer was used to measure the length of the children. The machines were calibrated every 6 months."

We have changed height to length in the revised manuscript where ever necessary.

6. Page 10: Morbidity per episode of any morbidity – what is the value of this description

Response: We thank the reviewer for this comment. We wanted to indicate the total number of days a child was ill during the two year follow-up. But now we have removed this sentence from the revised manuscript.

7. The authors have not mentioned what pre-natal maternal data are missing and reason for the missing data. Because of these missing data, risk factor analysis was done only on 216 children (over 50% loss).

Response: As described, the primary aim of the main study was to establish a birth cohort to study the natural history and immune response to Cryptosporidium spp. infection in children from birth to 3 years of age through intensive bi-weekly field worker visits. We took advantage of this carefully collected post-natal data and the limited, but still valuable, available pre-natal data to explore the possible effect of various pre- and post-natal factors on low birth weight, morbidity and growth of children living in an urban slum area with a high overall disease burden. Even though this study was not originally designed to capture the maternal pre-natal data, we obtained reliable information on maternal haemoglobin, last menstrual period (LMP), ante-natal visits (ANC), history of hypertension, diabetes, vaccination from the ante-natal cards. Health records of all mothers could not be obtained due to misplacement or loss or unclear recordings of the cards, which contributed to the missing data which was one of the limitations of this study. For future studies, we would like to recommend collection of maternal information pre-conception and throughout pregnancy. However in our study, a subgroup analysis verified the comparability between children with complete and without complete information. We found that both groups were very similar socio-demographically.
A sentence on the analysis has been added in the statistical analysis section in page 9, lines 197-200.

"The baseline demographic comparison was performed between children with and without prenatal maternal data was done using χ2 test or Fisher's exact test for categorical variables and two-tailed t-tests or Wilcoxon rank sum tests for continuous variables, depending on the distribution of the data."

Results of subgroup analysis are presented in supplementary material as Table S1, page 11, line 232-233 in the revised manuscript which now reads:

"Subgroup analyses between children with and without complete pre-natal maternal information demonstrated both groups did not differ socio-demographically (Table S1)."

8. The regression model needs to be described more clearly. What were the explanatory variables; what was the time window for each.

Response: The explanatory variables used in the regression models were time independent socio-demographic such as religion, maternal education, type of family, socioeconomic status, and antenatal/delivery/post-natal such as maternal anaemia, hypertension, diabetes, preterm birth, parity, history of abortion/still birth, duration of breast feeding. These variables are presented in Table 1. In addition, association of time dependent growth rate with overall morbidity was also explored. Multi variable analysis was performed using backward stepwise method. A parsimonious regression model was chosen considering the significance of predictors in the full model. As suggested by the reviewer, we have now added a paragraph explaining the explanatory variables and the model description on statistical analysis, which (page 10, lines 212-221) now reads:

"The explanatory variables used in the regression models were time independent socio-demographic variables such as religion, maternal education, type of family, socioeconomic status, and antenatal/delivery/post-natal variables such as maternal anaemia, hypertension, diabetes, preterm

birth, parity, history of abortion/still birth, duration of breast feeding. Factors identified in the univariate analysis at the significance level of 0.30 and clinically relevant variables were considered for inclusion in the full multivariate models. Multi variable analysis was performed using backward stepwise method. A parsimonious regression model was chosen considering the significance of predictors in the full model. For biological comparisons some non-significant variables, such as socio-economic status were retained in the final model where considered relevant."

9. The rationale behind choosing a significance level of .15 in the univariate analysis to consider in the multivariate analysis is not explained. As there may be some clinically relevant variables with significant level >0.15 in univariate analysis, incorporating those variables in the multivariate analysis could change the estimate of risk factors as this is an explanatory analysis.

Response: We appreciate the reviewer's comment. Based on the above comment and the suggestion from Prof. Nimbalkar, we have now re-run the multiple variable regression analysis by including variables significant at P ≤ 0.30, as well as clinically relevant variables (maternal anaemia, preterm birth, maternal literacy, maternal age and parity) in the full model. We then performed a backward stepwise regression analysis and eliminated the variables which contributed least to the overall explanatory capacity of the model. The final reduced model comprised of variables that remained significant in till the end. The results of this multivariable analysis did not vary from what was presented earlier in the manuscript.
The paragraph (page 10, lines 212-221) now reads:

"The explanatory variables used in the regression models were time independent socio-demographic variables such as religion, maternal education, type of family, socioeconomic status, and antenatal/delivery/post-natal variables such as maternal anaemia, hypertension, diabetes, preterm birth, parity, history of abortion/still birth, duration of breast feeding. Factors identified in the univariate analysis at the significance level of 0.30 and clinically relevant variables were considered for inclusion in the full multivariate models. Multi variable analysis was performed using backward stepwise method. A parsimonious regression model was chosen considering the significance of predictors in the full model. For biological comparisons some non-significant variables, such as socio-economic status were retained in the final model where considered relevant."

10. The authors have categorized many continuous variables to categorical variables without clear definitions such as number of household member, ANC visits, maternal age etc.

Response: We apologise for not giving an explicit explanation on the cut offs used to categorize continuous variables. The cut off for the number of ANC visits (≥4 or more visits), maternal anaemia (<10 gm%), exclusive breast feeding (6 months or more) were all based on WHO recommendations. We used a median cut off of 5 to categorize household members greater and lesser than 5 members. Categorization of the maternal age was based on whether the mother was a teenager (<20years) or over 20 years. We have now added these definitions in the Methods section of the revised manuscript (page 7, line 138-142), which reads as follows:

"Definitions of risk factors including number of antenatal care (ANC) visit of <4 [12], maternal anaemia (moderate-severe) with a cut off of <10 gm% [12] and exclusive breastfeeding for <6 months [13] were as specified by WHO. A median cut off of 5 was used to categorize households as those with equal to or lesser and greater than 5 members. The maternal age was categorized into teenage mothers (<20 years) or those at least or older than 20 years."

11. As standard definitions for morbidity were not used, it may be difficult to generalize the findings to other settings.

Response: According to IMCI and IMNCI guidelines, in settings with limited access to health care, the health workers have to assess, classify and manage childhood illnesses for which they need to follow the IMCI/IMNCI standard definitions, whereas in our study, field workers were trained to only identify mild common illnesses such as diarrhoea, cold, cough and fever by using a "standard" field definition. Sick children were routinely referred to the study clinic, where the illness was confirmed and managed by a study physician/paediatrician. Severity of illness was also assessed by the same physician who referred children with severe illnesses to hospital, if needed. Hence we believe, where access to healthcare is reasonable and physicians are available, a field definition for mild illnesses complemented by the physician diagnosis for severe illness for capturing total morbidity in a population is an appropriate and a feasible option.

Reviewer #2:

Reviewer Name: Prof. SomashekharNimbalkar
Institution and Country head, Central Research Sciences
CharutarArogyaMandal,
Karamsad-Anand-Gujarat
Please state any competing interest or state 'None declares': None declared

1. Summary: The study is a well-designed, relevant and appropriately conducted and worthy of publication. However the discussion is less engaging than you would expect from the scope of the study, especially from the Public Health viewpoint.

Response: We thank the reviewer for this comment. As per the suggestion, we have now extensively modified and expanded our discussion section, highlighting the relevance of our findings from the public health perspective.
The modified Discussion (pages 14-17, lines 305-382) now reads:

"This study reported 98% institutionalized deliveries in a poor to middle class urban slum area in southern India, much greater than the reported national estimate of 39% in NHFS-3 data,[17] reflecting a rapid hastening of the change of practice following the institution of conditional cash transfers under the Janani Suraksha Yojana or JSY scheme.[18] This has indirectly led to more antenatal visits, likely improving awareness of good antenatal care and health seeking behaviour during pregnancy, and thereby improving maternal and neonatal survival which, in turn, is reflected in the lack of early neonatal deaths and the lower proportion of low birth weight in this study (17%) as compared to the national average of 22%.[17]
Antenatal checkups are important for screening of high risk mothers, monitor weight gain during pregnancy, screen for anaemia; provide nutritional supplements that are vital for good pregnancy outcome, and help reduce and/or prevent maternal and neonatal complications and mortality. Studies have demonstrated that increasing number of ANC visits coupled with good quality antenatal care reduces the likelihood of having low birth weight babies.[19-21] In this study, children born to the mothers with fewer than 4 antenatal visits had 6 times greater odds of low birth weight; also children born preterm were three times more likely to be low birth weight, similar to previous reports from Tanzania and India.[22-24] Birth weight is an important health indicator for vulnerability to childhood illnesses and survival. Low birth weight has been linked to higher mortality and morbidity[25], impaired mental development[26], and the risk of chronic adult diseases such as cardiovascular diseases and diabetes in later days of life.[27] [28]
In developing countries, over 50% of pregnant women are anaemic,[29] which reflects inadequate maternal nutritional status with respect to iron, folic acid and other nutrients which could be picked and managed during the ANC visits. In this study, mothers with hemoglobin less <10 gm/dL during pregnancy had twice the risk of having low birth weight babies. Studies elsewhere [30-32] have also demonstrated the negative effect of maternal anaemia on birth weight. A study in Pakistan reported

64% low birth among anemic mothers compared to only 10% in non anemic mothers. [33] Taken together, these findings highlight the importance of at least 4 regular antenatal check-ups, as recommended by WHO [12].

Among all childhood morbidities, respiratory and diarrhoeal diseases are the major causes of morbidity among children in India [15, 34-35] and other developing countries.[36-37] Children in this cohort also suffered predominantly from respiratory and GI illness. These estimates were very similar to the previous studies conducted in the same environment in the past decade for all illnesses, respiratory and GI disease. [15] [35]. The high estimates of GI illness can be attributed to widespread contamination of the drinking water supply which has been documented previously by other studies conducted in the same area [38]. In order to tackle this problem, there should be promotion for improvement in water, hygiene and sanitation systems in developing countries.

The child's age had an inverse effect on overall and GI illnesses [35, 39], although respiratory illness increased with age. This may possibly be due to an increase in allergic airway disease. [40] Studies have documented that children from low socio-economic status were at higher risk for morbidity because of the lack of basic amenities needed to lead a healthy life.[41-42] Children from households where firewood was used as the main fuel had a higher risk of illness in this study. Firewood can be considered an indicator for low socio-economic status and also as an ambient pollutant and allergen that increases risk for respiratory illness in children. [43-45] This highlights the impairing effect of indoor and outdoor air quality on upper respiratory illnesses. Provision of cost effective clean alternative fuel and properly designed ventilated houses to marginalized communities such as slum dwellers can minimize this burden.

Girls were protected from overall, GI and respiratory illnesses as compared to boys. Similar findings have been identified in various studies conducted in India and elsewhere,[41, 46] [35, 47] which can be attributed to biological differences in gender. However, the growth rates in terms of average monthly height and weight gain were lower in girls, similar to a report from Brazil.[48] This could be because of social factors such as the preferential care and nutrition that a boy receives in developing countries [49]. With provision of proper nutrition to girls and with an added biological advantage over boys, girls could develop and perform better than they do currently. Frequent reinforcement of girl child equity and creation of community awareness towards child rights as advocated by the United Nations in the Convention of Child Rights can help bring changes in social practices and beliefs.

WHO recommends exclusive breast feeding for 6 months of life for child survival [13]. Human milk glycans are part of the natural immunological mechanism that offers protection against diarrhoeal diseases in breastfed infants [50]. In addition, breast feeding reduces the exposure to contaminated foods and liquids and contributes to adequate nutrition and non specific immunity. Our data showed approximately 20-25% protection against overall morbidity and acute respiratory illness among children who were exclusively breastfed for 6 months. Although breastfeeding offered some protection against GI morbidity, it was not statistically significant. The lack of protection in this study may be a reflection of overall high rates of breastfeeding. Reviews on breastfeeding have determined the protection offered by exclusive breastfeeding against diarrhoea [50-51] respiratory infections [52] and for child survival.[47, 53]

Interestingly, average monthly height and weight gain had an inverse relationship with duration of breastfeeding. Children exclusively breastfed for 6 months had slower growth rates in terms of height and weight over two year period when compared against children who started weaning early. Studies done elsewhere, also documented the slower growth pattern among children with prolonged period of exclusive breastfeeding than children on formula food or non-human milk. [48, 54-55] [56]

Even with economic barriers, provision of good quality health care can improve the health seeking behaviour of people, which was reflected in this study by the high number of clinic/hospital visits. Timely intervention can prevent or slow the progression of the disease, thereby reducing complications and death. The higher than reported hospitalization rates in this and previous community-based surveillance studies from Vellore [15, 35] possibly reflect an unmet need for hospitalization in resource-constrained settings.

2. Strengths: Well defined cohort, very few lost to follow up, Study variables defined sufficiently and hence it is replicable.
Minor: Page 4, Line 80 – Use word "Economic status instead of poverty.

Response: We thank the reviewer for his comment. The word "poverty" has now been changed to "economic status" in the revised manuscript (page 4, line 80).

3. Almost 50% morbidity is due to respiratory diseases, crowding, in house smoke (40% using firewood), and environmental exposures (Beedi making). These are not explored in detail. If data is available these may be explored further (unless a separate manuscript is being planned)

Response: We thank the reviewer for this suggestion. We had done the analysis to explore the factors associated with respiratory illnesses but, due to space constraints, presented the results as Supplementary table S2b. There was significant risk of respiratory illness associated with the use of firewood as primary fuel, but not with beedi making at home. This has been mentioned in results section (page 13, line 282-285).

"Although female gender (0.76, 0.57–1.03) and exclusive breasting feeding for six months (0.76, 0.52–1.10) were protective, they were not statistically significant, whereas usage of firewood as the main fuel, a proxy for low socioeconomic status, was associated with increased risk of GI (1.52, 1.11-2.08) and respiratory (1.10, 1.00-1.21) illness (Tables S2a and S2b)."

4. It is evident that the p values changed significantly for some variables in multivariable analysis as compared to univariate analysis. It is interesting to see what emerge if factors with p less than 0.3 are included in the model (as numbers of observations are adequate for such model).

Response: We are thankful to the reviewer for this suggestion. Based on this and the comments from Dr. Bhandari, we have now repeated the multivariable analyses keeping the factors with p ≤ 0.3 and also including the clinically relevant variables (maternal anaemia, preterm birth, maternal literacy, maternal age and parity).The findings of this analysis did not differ from what was reported earlier.

5. It is interesting to observe good health seeking behaviour (98% institutional deliveries) despite risk of losing daily wages. Other studies found poor health seeking behaviour in urban slums. Is it due to financial independence that women enjoy in this region?

Response: It is true that people in the study area have good health seeking behaviour. The high rate of institutional deliveries is mostly because of the proper functioning and awareness of the conditional cash transfer (CCT) programme, Janani Suraksha Yojana (JSY) in Tamil Nadu. The high rate of clinic/hospital visits in this study was mostly due the fact that parents/primary caregivers were encouraged to bring sick children to the study clinic (located within the study area), whenever possible. The study clinic provided free treatment for all under-five children in that area. The high hospitalization rates observed in this study is possibly a reflection of the unmet need for hospitalization in children living in resource poor settings. This has now been included in the Discussion section (page 14, lines 305-312 and page 17, lines377-382).

6. There seems to be confusion between multivariate and multivariable. Multivariate typically implies more than two dependent variables. It is recommended to use 'multivariable' consistently.

Response: We thank the reviewer for this suggestion and have replaced the word "multivariate" with "multivariable" throughout the revised manuscript.

7. Diarrheal diseases and pneumonia are leading causes of morbidity and mortality in children. This is a well known fact. Even availability of potable water can reduce upto 30% disease burden in children. So the study does not show any new findings. But they are still relevant as they depict the picture in current scenario and provide guidance to policy makers and academic community on research arenas in this field. The discussion can be improved by incorporating public health interventions – current and potential ones that can be considered to address these issues. Discussion appears a replication of results and findings are compared to other studies. it does not delve enough into possible causes and potential solution.Relevance of the study to current scenario in India needs to be discussed in detail. Discussion section is the one which needs to be improve tremendously.

Response: We thank the reviewer for this comment. We have now extensively modified the Discussion section and provided an analysis of the possible causes of the high incidence of respiratory and diarrhoeal morbidity among the study children and potential solutions to reduce the same. We have also highlighted the public health significance of the findings from the risk factor analysis and outlined specific public health interventions that can help counter this risk and thereby reduce the high disease burden in Indian slum children. The revised Discussion is presented on pages 14-17, lines 305-382.

VERSION 2 – REVIEW

REVIEWER	Prof. Somashekhar Nimbalkar Department of Pediatrics, Pramukhswami Medical College, Karamsad-Anand-Gujarat-India.
REVIEW RETURNED	09-Jun-2014

| GENERAL COMMENTS | Summary: The authors have changed most of the paper as per the reviewers suggestions and argued well when they have not agreed. However there are many minor corrections that need to be made with a few important ones in discussion which are detailed below. Abstract: In participants we cannot start with a number. Replace 497 by words.
Throughout the manuscript numbers less than 10 are written as figures. Traditionally these are written in words.
Line 82: Remove 'also'.
Line 307: How can comparison to the national estimate reflect a change in practice? As pointed out by authors this is not a regular slum as their healthcare seeking behavior is much better than the average. It is highly possible that even 10 years earlier the rate would have been the same. Either there should be some comparable data from the same area (either from a study or government data available locally) or "reflecting a hastening of change" needs to be reframed.
Line 312: Same comment as above.
Line 319: "also children born preterm were three times more likely to be low birth weight". Most preterms are usually low birth weight. While all low birth weight may not be preterm. Though the statement may be factually correct it is a known clinical knowledge. This may be reframed or removed from the discussion while ensuring that it remains in the results or tables.
Line 326: the word 'picked' may be changed to detected. However while the statement looks reasonable to say "iron, folic acid and other nutrients can be detected and managed" it seems that the investigators are not aware of the tremendous costs of identifying these deficiencies. The current management scenario where these are considered present if anemia is there and managed is a more reasonable strategy. This may be added to the discussion.
Line 342: "This may be possibly be due to an increase in allergic |

airway disease". This is purely speculative with the reference 40 being a reference from a study from the states. It is well known that the allergy scenario in India is not well known but is considered to be different from the US. The current study also looked at environmental factors such as smoke, etc which also could have played a role and is mentioned in the discussion. Hence the above line can be rewritten in a different place with preferably a reference from the developing world.

Line 358 to 360: "Frequent reinforcement of girl child equity and creation of community awareness towards child rights as advocated by the United Nations in the Convention of Child Rights can help bring changes in social practices and beliefs". This statement does not have a reference. Also it seems too simplistic. Social change cannot be brought about by just creation of community awareness. This statement needs to be reframed or referenced in such a way that it does not seems like a simple solution. Or it may be removed.

VERSION 2 – AUTHOR RESPONSE

Summary: The authors have changed most of the paper as per the reviewer's suggestions and argued well when they have not agreed. However there are many minor corrections that need to be made with a few important ones in discussion which are detailed below.

Comments:
1. Abstract: In participants we cannot start with a number. Replace 497 by words.
Throughout the manuscript numbers less than 10 are written as figures. Traditionally these are written in words.

Response: We thank the reviewer for this comment and suggestion. We have now replaced numeric 497 by words in the abstract. Throughout the manuscript wherever needed, we have now presented all the numbers less than 10 in words.

2. Line 82: Remove 'also'.

Response: The word "also" from line 82 has now been removed.

3. Line 307: How can comparison to the national estimate reflect a change in practice? As pointed out by authors this is not a regular slum as their healthcare seeking behavior is much better than the average. It is highly possible that even 10 years earlier the rate would have been the same. Either there should be some comparable data from the same area (either from a study or government data available locally) or "reflecting a hastening of change" needs to be reframed.
Line 312: Same comment as above.

Response: We thank the reviewer for this comment. We have now modified the paragraph and compared our data with the Tamil Nadu state estimates from NFH3 data (page 14, line 305-313).

"The introduction of conditional cash transfers for institutional deliveries under the Janani Suraksha Yojana or JSY scheme in 2005 has resulted in an increase in the proportion of institutional deliveries increased in the state of Tamil Nadu from 79.3% in 1998-99 to 90.4% in 2005-06. [1718] In this study as well, 98% of the mothers delivered in an institutional facility. This change of practice has indirectly led to more antenatal visits, likely improving awareness of good antenatal care and health seeking behaviour during pregnancy, and thereby improving maternal and neonatal survival which, in turn, is

reflected in the lack of early neonatal deaths and the lower proportion of low birth weight in this study (17%) as compared to the national average of 22%,but similar to the Tamil Nadu average of 17.2%. [17]"

4. Line 319: "also children born preterm were three times more likely to be low birth weight". Most preterms are usually low birth weight. While all low birth weight may not be preterm. Though the statement may be factually correct it is a known clinical knowledge. This may be reframed or removed from the discussion while ensuring that it remains in the results or tables.

Response: We thank the reviewer for this comment and suggestion. We have now removed the sentence "also children born preterm were three times more likely to be low birth weight" from the manuscript, but retained the information in the results and tables.

5. Line 326: the word 'picked' may be changed to detected. However while the statement looks reasonable to say "iron, folic acid and other nutrients can be detected and managed" it seems that the investigators are not aware of the tremendous costs of identifying these deficiencies. The current management scenario where these are considered present if anaemia is there and managed is a more reasonable strategy. This may be added to the discussion.

Response: We thank the reviewer for this comment. We would like to clarify that authors wanted to convey that deficiency of iron, folic acid and other nutrients attributed to anaemia in pregnant women in developing countries identified during routine ANC visits, can be detected and managed. We have now restructured page 15, line 325-328, as follows.

"In developing countries, over 50% of pregnant women are anaemic,[29] which reflects inadequate maternal nutritional status with respect to micronutrients. Routine ANC visits will result in early detection of anaemia, which can then be managed through iron and folic acid supplements and appropriate nutritional advice."

6. Line 342: "This may be possibly due to an increase in allergic airway disease". This is purely speculative with the reference 40 being a reference from a study from the states. It is well known that the allergy scenario in India is not well known but is considered to be different from the US. The current study also looked at environmental factors such as smoke, etc which also could have played a role and is mentioned in the discussion. Hence the above line can be rewritten in a different place with preferably a reference from the developing world.

Response: We thank the reviewer for this comment. We have now reframed the paragraph and have provided a reference of a study which was conducted in India describing respiratory allergies in the children (Kumar et al., Asian Pac J Allergy Immunol.,2008,26:213-22). The paragraph (page 16, lines 343-349) now reads:

"The child's age had an inverse effect on overall and GI illnesses [35, 39], although respiratory illness increased with age. Studies have documented that children from low socio-economic status were at higher risk for morbidity because of the lack of basic amenities needed to lead a healthy life.[40-41] Children from households where firewood was used as the main fuel had a higher risk of illness in this study. Firewood can be considered an indicator for low socio-economic status and also as an ambient pollutant and allergen that increases risk for respiratory illness and allergic airway diseases in children. [42-45]"

7. Line 358 to 360: "Frequent reinforcement of girl child equity and creation of community awareness towards child rights as advocated by the United Nations in the Convention of Child Rights can help bring changes in social practices and beliefs". This statement does not have a reference. Also it

seems too simplistic. Social change cannot be brought about by just creation of community awareness. This statement needs to be reframed or referenced in such a way that it does not seems like a simple solution. Or it may be removed.

Response: We thank the reviewer for this comment. We have now removed that sentence from the manuscript.